II. REMARKS

Preliminary Remarks:

New claims 44-64 are submitted in place of the previously pending claims, which are canceled.

Independent claim 44 is directed to the disclosed method of treating cancer comprising administering to a patient (a) an admixture comprising a cancer or tumor antigen expressed by the cancer cells and a microfluidized antigen formulation comprising (i) a stabilizing detergent, (ii) a micelle-forming agent, and (iii) a biodegradable and biocompatible oil, in combination with (b) a therapeutically effective amount of at least one agent which is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFβ specifically, wherein the antigen-containing admixture and the inhibitor of TGFβ production or activity are administered sequentially or concurrently, and in any order. New dependent claims 45-64 are directed to disclosed embodiments of the method of claim 44.

The method of treating cancer of claim 44 is described in the specification, for example, at page 4, line 8, to page 5, line 5, and at page 6, line 6, to page 10, line 2. The method wherein the cancer antigen is selected from the antigens in new claim 49 is described on pages 13-14, and treatment of cancers of the types specified in new claim 50 is described on page 15, lines 13-18. Co-administration of an agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFβ specifically is described, for example, at page 4, lines 20-24. New claims 51-64 specify concentrations and specific types of stabilizing detergents, micelle-forming agents, and oils that are suitable for the claimed invention, as described on page 11, line 4, to page 12, line 8, and the disclosed examples. The presence of less than 20 micrograms of an immunostimulating peptide or the absence of such a peptide in the antigen-containing admixture as specified in claims 63 and 64 is described on page 12, lines 9-16. The subject matter of the new claims is also found in original claims 1-37 of the parent application, U.S. Application No. 08/933,359, the contents of which are incorporated into the present application.

Patentability Remarks:

Objections

The official action objected to claim 29 because it depended on canceled claim 27, and objected to claims 38-42 because these claims were considered to be substantial duplicates of claims 23-26 and 29.

Claims 29 and 38-42 are canceled, and the applicants submit that the new claims that are submitted herewith are not subject to the objections to claims 29 and 38-42 that were stated in the office action.

35 U.S.C. §112, Second Paragraph

Claims 32-33 and 43 were rejected under 35 U.S.C. §112, second paragraph, because they were considered to be vague and indefinite.

(a) Claim 32 was rejected because the term "said cancer cells" was considered to be without sufficient antecedent basis.

New claim 44, which corresponds closely to the subject matter of claim 32, is directed to a method of treating cancer comprising administering to a patient in need thereof an admixture that comprises a cancer or tumor antigen that is expressed by cells of the cancer to be treated. The applicants submit that the precise meaning of the reference to cancer cells in new claim 44 is clear and unambiguous.

(b) Claim 43 was rejected because it was considered to be unclear whether the term "said antigen" in claim 43 referred to the antigen in the admixture that is administered, or to the antigen of the "antigen-specific" CTL response.

New claim 49, which corresponds closely to canceled claim 43, clearly specifies that the selected antigen is a cancer or tumor antigen that is present in the antigen-containing admixture of claim 44.

In view of the foregoing, withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

35 U.S.C. §112, first paragraph

Claims 23-26, 29, 32-34, and 38-43 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that the specification allegedly fails to provide adequate written description of any method for treating cancer other than a method wherein the cancer antigen is papillomavirus E7 protein and the agent that antagonizes an immunosuppressive factor is an anti-TGFβ antibody.

The applicants respectfully traverse the ground of rejection. The office action acknowledges that the application discloses a number of known cancer-specific antigens that it describes as being suitable for use in the antigen-containing admixture of the claimed method, for eliciting a therapeutic antigen-specific CTL response. The office action also acknowledges that the application describes five different tumor and host-secreted immunosuppressive factors that help cancer cells avoid immune destruction in a patient with cancer. The office action further acknowledges that the application describes a working example of the claimed invention, in which the cancer antigen is the cancer-associated papillomavirus E7 protein, the immunosuppressive factor is TGFβ, and the agent that antagonizes TGFβ is an anti-TGFβ antibody.

As the rationale in support of the rejection, the examiner alleges:

(i) that "the disclosure only *reasonably* conveys possession of an anti-cancer composition comprising anti-TGFβ antibodies in conjunction with E7-PROVAX^{TM}," which is the combination demonstrated in the disclosed working example; and

(ii) that the application "fails to adequately describe the claimed genus of antagonists and antigens" because the individual cancer antigens and antagonists described in the specification are highly variant, and that

(a) the disclosed working examples demonstrate the therapeutic efficacy of only one combination of cancer antigen and immunosuppressive factor antagonist, and

(b) the written description fails to describe "structural or functional features" that "distinguish the claimed genus of antagonists and antigens from other molecules that do not have the claimed biological properties."

The applicants respectfully submit that the office action is incorrect in its representation of the manner in which one of skill in the art would understand the description of the invention provided by the application.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement (Fed. Reg., Vol. 66, No. 4, Jan. 5, 2001) state that the statement of the rejection must accord with a thorough reading and evaluation of the application, and must present evidence or reasons why one of skill in the art would not recognize that the written description of the invention provides support for the claim (see p. 1105).

With regard to assessing whether a skilled person would have regarded the applicant as being in possession of the claimed invention, the guidelines state that,

> "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." (*Id.*, page 1106)

The guidelines further state that

> "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. (ref. omitted)) If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." (ref. omitted) (*Id.*, page 1106).

For the reasons discussed below, the applicants submit that the application as filed adequately described the claimed invention with sufficient technical detail that a person of

skill in the art of cancer immunotherapy would reasonably have considered that the applicants were in possession of the claimed invention at the time of filing.

The application describes the claimed method as a method for treating cancer that comprises administering to a patient with cancer:

> (a) an admixture comprising a cancer or tumor antigen expressed by the patient's cancer cells and a microfluidized antigen formulation comprising a stabilizing detergent, a micelle-forming agent, and a biodegradable and biocompatible oil,

in combination with:

> (b) a therapeutically effective amount of at least one agent which is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFβ specifically,

wherein the antigen-containing admixture and the TGFβ-inhibiting agent are administered sequentially or concurrently, and in any order.

At the time the application was filed, persons of skill in the art would have recognized that a CTL response can be elicited effectively against a cancer-specific antigen in a cancer patient by administering to the patient an admixture comprising a cancer or tumor antigen expressed by the patient's cancer cells, and a microfluidized antigen formulation comprising a detergent, a micelle-forming agent, and oil, according to the claimed invention. For example, see International Publication No. WO 96/17683, published June 13, 1996, and U.S. Patent No. 5,695,770, cited herein. Both of these documents disclose examples that demonstrate the successful elicitation of CTL responses with adjuvant admixtures according to the claimed invention that contain albumin and viral gp120 proteins as experimental antigens.

At the time of filing, persons of skill in the art recognized that the cellular system for degrading, processing, and presenting antigens as complexes with MHC class I protein was a general system capable of specifically presenting antigenic peptides of essentially any antigenic protein introduced into the cytoplasm of an antigen-presenting cell. That this view was widely held by persons skilled in the art is evidenced by the broad conclusions drawn by researchers in the field regarding the mechanisms of antigen processing and presentation based on experimental studies with a single antigen. For example, from their experiments in which albumin is used as an antigen, Carbone et al. (J. Exp. Med., 1990, 171:377-387, copy

attached) drew the generalized conclusion that "class I-restricted processing and presentation of exogenous antigen can occur in vivo following immunization with cell-associated antigen" (see pages 385-386). Moore et al. (Cell, 1988, 54:777-785, copy attached) broadly concluded from their research in which albumin is used as an antigen that "the technique of loading cells should enable us to immunize class I restricted CTL *against any soluble protein*" (p. 783, emphasis added). Takahashi et al. (Nature, 1990, 344:873-875, copy attached) concluded from their studies of inducing MHC class I-restricted CTL responses with immunostimulating complexes (ISCOMS) containing gp160 antigen that "ISCOM-based vaccines may achieve the long-sought goal of induction of both CTL and antibodies by a purified protein" (p. 875). Accordingly, at the time of filing, a person of skill in the art would have regarded the successful induction of MHC class I-restricted CTL responses with an adjuvant containing an experimental antigen such as albumin or viral gp120 as sufficient evidence that similar results would reasonably be expected using the claimed adjuvants which contain different antigenic proteins.

This view has been upheld by the U.S. Patent and Trademark Office, which issued the following patents with claims (copies attached) directed to methods and compositions useful for inducing a CTL response (CTL) in a human comprising providing the antigen to which the CTL response is desired and an antigen-containing admixture such as that of the present invention:

1) U.S. Patent No. 5,585,103, which issued December 17, 1996, claim 1 of which is directed to:

> "A method for inducing an immunotherapeutic cytotoxic T-lymphocyte response against cancer or virally infected cells in an animal ...[that]...comprises cancer or virally infected cells, comprising: administering to said animal an admixture comprising a cancer antigen or viral antigen expressed by said cancer or virally infected cells and a microfluidized antigen formulation ...comprising ...[a detergent, a micelle-forming agent, and an oil] ... administered to said animal in an amount sufficient to induce a cytotoxic T-lymphocyte response in said animal which is specific for the viral or cancer antigen contained in said admixture."

2) U.S. Patent No. 5,695,770, which issued December 9, 1997,

3) U.S. Patent No. 5,706,860, which issued January 20, 1998, and

4) U.S. Patent No. 6,197,311, which issued March 6, 2001.

Each of these patents was granted claims directed to methods similar to the method of claim 1 of U.S. Patent No. 5,585,103, wherein the admixture that is administered to elicit a CTL response contains antigens other than those of the disclosed working examples.

In view of the foregoing, it is clear that persons of skill in the art reasonably expected antigen-containing admixtures according to the claimed invention that contain a cancer or tumor antigens to be capable of eliciting a CTL response against the antigen in a human subject. In fact, a brief review of the published scientific literature shows that most, if not all of the specific cancer antigens disclosed in the specification have been shown to be capable of eliciting cancer cell-specific immune responses in experimental immunotherapy protocols.

At the time of filing, persons of skill in the art also recognized that each of the types of cancer identified in the present application as being treatable by the claimed invention appears to be associated with increased levels of TGFβ, which generally inhibits the profileration of normal, non-cancerous cells: For example, see the attached abstracts of following references for the corresponding cancers:

breast cancer: Ivanovic et al., Eur J Cancer. 2003 Mar;39(4):454-61.

brain cancer: Seoane et al., Cell. 2004 Apr 16;117(2):211-23.

cervical cancer: Lee et al., Int J Cancer. 2001 Nov15;94(4):500-7.

leukemia: Schiemann et al. Cancer Detect Prev. 2004;28(1):57-64.;

lymphoma: Matsunaga et al., Ann Hematol. 2004 May;83(5):322-5. Epub 2003 Nov 11.

prostate cancer: Shariat et al., J Clin Oncol. 2001 Jun 1;19(11):2856-64;

skin cancer: Medrano et al., Oncogene. 2003 May 19;22(20):3123-9.

colon cancer: De Wever et al., J Cell Sci. 2004;117(Pt 20):4691-4703. Epub 2004 Aug 25.

lung cancer: Hasegawa et al., Cancer. 2001 Mar 1;91(5):964-71.

ovarian cancer: Xi et al., J Huazhong Univ Sci Technolog Med Sci. 2004;24(1):62-5.

pancreatic cancer: Subramanian et al. Cancer Res. 2004 Aug 1;64(15):5200-11.

liver cancer: Sacco et al., Cytokine. 2000 Jun;12(6):811-4.

bladder cancer: Shariat et al., Cancer. 2001 Dec 15;92(12):2985-92.
kidney cancer: Mitropoulos et al., Urol Res. 2004 Sep 7 [Epub ahead of print]
myeloma: Brown et al., Br J Haematol. 2004 Jun;125(6):743-8;
colorectal cancer: Xiong et al., World J Gastroenterol. 2002 Aug;8(4):674-8.
nasopharyngial carcinoma: Xu et al., Int J Cancer. 1999 Aug 20;84(4):396-9.
endometrial cancer: Piestrzeniewicz-Ulanska et al., Oncol Rep. 2003 Sep-Oct;10(5):1539-44.

The specification teaches that TGFβ has immunosuppressive activity (see pages 7-8), and describes specific types of agents that may be used to specifically neutralize, block, antagonize, or down regulate the activity or prevent the activation of TGFβ (see pages 8-9). The disclosed methods are well-known, routine approaches for preventing the occurrence of a receptor-ligand interaction, and persons of skill in the art would reasonably expect the disclosed methods for inhibiting TGFβ production or activity to operate effectively.

In addition, the present application demonstrates the surprising result that the claimed combination of antigen formulation and an agent that neutralizes or down-regulates TGFβ elicits a therapeutic immune response in a mammal that is significantly greater that the sum of the effects of the individual agents. For example, the disclosed example shows that treatment of experimental animals with tumors that express the ovalbumin antigen with an antigen formulation prepared according to step (a) of claim 1, in combination with an inhibitor of TGFβ, elicits potent anti-tumor activity, whereas treatment with the antigen formulation alone is ineffective (see page 16, lines 18-22, and Figure 1, in Example 1). Example 2 similarly describes enhanced anti-tumor activity following co-administration of an tumor-associated viral antigen formulation prepared according to step (a) of claim 1 and an inhibitor of TGFβ activity (anti-TGFβ antibodies) (see page 18, lines 6-8, and Figures 2A and 2B). Prior to the disclosure of the claimed invention in the present application, the therapeutic synergism shown by the CTL-inducing vaccine in combination with an agent for neutralizing, antagonizing, down-regulating, or blocking TGFβ was unknown and unexpected. In view of the successful demonstration of anti-tumor synergism of the claimed invention in vivo against tumors producing two highly dissimilar antigens (ovalbumin and HPV-E7 protein), persons of skill in the art would reasonably expect that other combinations of antigen and TGFβ antagonist would operate in a similar, successful manner.

In view of the foregoing, the applicants submit that one of skill in the art would consider the applicants to have been in possession of the claimed invention at the time of filing, and withdrawal of the rejection of the claimed invention under 35 U.S.C. §112, first paragraph, for lack of written description is respectfully requested.

35 U.S.C. § 102(e)

Claims 23-26, 29, and 38-43 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Berd et al. (U.S. Patent Application No. 2002/0004052). Berd et al. describes a method for treating cancer comprising pretreating a patient with a low dose of cyclophosphamide, and then administering a composition comprising a cell surface antigen of the cancer to be treated in order to elicit a T cell-mediated immune response against the cancer cells, For example, see paragraphs [0009], [0046], and [0096]. The official action also cites Matar et al. (Eur J Cancer. 2000 May;36(8):1060-6), which reports that low dose cyclophosphamide treatment inhibits the production of TGF-beta, interleukin-10 (IL-10) and nitric oxide (NO) and promotes spleen lymphoproliferative responses in lymphoma tumor-bearing rats.

The present claims are directed to a method for treating cancer comprising administering to a patient with a cancer: (a) an admixture comprising a cancer or tumor antigen expressed by cells of the cancer and a microfluidized antigen formulation comprising: a stabilizing detergent, a micelle-forming agent, and a biodegradable and biocompatible oil, in combination with: (b) a therapeutically effective amount of at least one agent which is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFβ specifically. **Berd et al. does not describe the antigen-containing admixture of the claimed invention**. Moreover, cyclophosphamide is an alkylating agent that broadly inhibits the production of multiple cytokines, whereas the claimed invention comprises administering an agent that acts specifically against TGFβ. The claimed invention therefore is not anticipated by the patent of Berd et al., and withdrawal of the rejection of claims under 35 U.S.C. § 102(e) is respectfully requested.

35 U.S.C. § 103(a)

Claims 23-26, 29, 32-34, and 38-43 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable in view of Raychaudhuri et al. (U.S. Patent No. 5,695,770), in combination with Berd et al. (U.S. Patent Application No. 2002/0004052) and Berd et al. (Cancer Research, Vol. 46, May 1986, pp. 2572-7).

Raychaudhuri et al. describes a method for inducing a CTL response against cancer cells in a patient suffering from cancer, comprising administering to the patient an admixture comprising a cancer antigen expressed by cells of the cancer and a microfluidized antigen formulation comprising a stabilizing detergent, a micelle-forming agent, and a biodegradable and biocompatible oil. Thus, Raychaudhuri et al. describes the first step of the presently claimed method - administering an admixture comprising a cancer or tumor antigen that is capable of eliciting a CTL response against the cancer antigen. However, neither Raychaudhuri et al. nor either Berd et al. reference describes or suggests administering the antigen-containing admixture of the invention in combination with a therapeutically effective amount of an agent that capable antagonizes TGFβ specifically.

The Berd et al. patent describes a method for treating cancer comprising pretreating the patient with cancer with a low dose of cyclophosphamide, and then administering to the patient a composition comprising a cell surface antigen of the cancer to be treated, which composition is capable of eliciting a T cell-mediated immune response against the cancer cells. The patent states that the effect of the cyclophosphamide pretreatment is to reduce the function of peripheral blood lymphocyte non-specific T suppressor cells (paragraph [0009]).

The Berd et al. article (Cancer Research, Vol. 46, May 1986, pp. 2572-7) reports that pretreatment of a subject with cancer with a low dose of cyclophosphamide prior to administering a composition comprising a cell surface antigen of said cancer results in a greater T cell-mediated immune response against the cancer cells than is achieved in the absence of the cyclophosphamide pretreatment. The reference also teaches that the effect of the cyclophosphamide pretreatment is to deplete or functionally impair suppressor T cells that otherwise suppress the immunological response to the tumor antigens (see p. 2572).

As discussed above, the claimed invention is a method for treating cancer comprising administering to a patient with a cancer (a) an admixture comprising a cancer or tumor

antigen expressed by cells of the cancer, which admixture is capable of eliciting a CTL response that is specific for the antigen, in combination with (b) a therapeutically effective amount of at least one agent which is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFβ specifically.

The patent and publication of Berd et al. teach that pretreatment with cyclophosphamide is performed in order to reduce the activity of suppressor T cells, as discussed above. Cyclophosphamide is an alkylating agent that inhibits the expression of multiple cytokines, and is not capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFβ specifically, as discussed above. In addition, both Berd et al. references taught that the basis for the immunopotentiating effect of cyclophosphamide is the reduction in the activity of suppressor T cells. Accordingly, the prior art neither described nor suggested the claimed invention to one of ordinary skill in the art, and withdrawal of the rejection of claims under 35 U.S.C. § 103(2) is respectfully requested.

The examiner observed that a reference of Matar et al. that was published in 2000 reported that cyclophosphamide can inhibit the production of TGFβ, IL-10, and nitric oxide in lymphoma tumor-bearing rats, as noted above. However, one of skill in the art would not consider the effects of cyclophosphamide on TGFβ to be so clear-cut. For example, Takiguchi et al. report that cyclophosphamide pretreatment of tumor-bearing mice has no effect on the level of TGFβ RNA in tumor tissues of the treated mice (Anticancer Res. 2004, 24(3a):1823-8, abstract attached). Moreover, Lian et al. (Neurosci. Lett. 2003, 35(1):51-55, abstract attached) and Weiner et al. (Mult. Scler. 2002, 8(2):142-154, abstract attached) report that cyclophosphamide **increases** TGFβ expression and activity in mice and humans, respectively. Therefore, it cannot be assumed that cyclophosphamide inherently reduces TGFβ production and/or activity in vivo. On this point, it is significant that Matar et al. reported in 2001 that "[t]he high level of IL-10 produced by T-cells from tumor-bearing rats is responsible for the inhibition of lymphocyte proliferation." The 2001 reference of Matar et al. further stated that "our results suggest that the shift from immunosuppression to immunopotentiation induced by treatment of tumor-bearing rats with a single low-dose of Cy [cyclophosphamide] is mediated by a reduction in T-cell derived IL-10 production, which

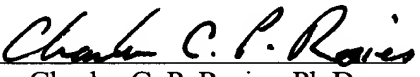
would account, to some extent, for the antimetastatic effect of Cy treatment." (See Int Immunopharmacol. 2001 Feb;1(2):307-19, abstract attached). From this reference, it is clear that the effect of cyclophosphamide treatment on cytokine expression that Matar et al. consider to be significant with regard to immunopotentiation is a reduction in T-cell derived IL-10 production, rather than any effect on TGFβ production or activity.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP, LLP

By 

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Attachments:

Attached hereto are:

1. Copies of the claims of following U.S. patents cited in the response:

   a) U.S. Patent No. 5,585,103,

   b) U.S. Patent No. 5,695,770,

   c) U.S. Patent No. 5,709,860, and

   d) U.S. Patent No. 6,197,311

2. A Form PTO-1449 citing scientific articles cited in the response;

3. Copies of scientific articles cited in the response, or their abstracts.